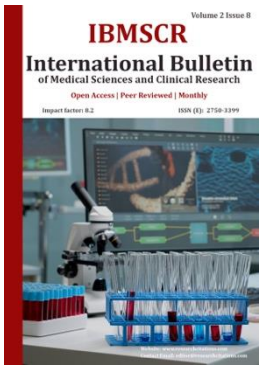

PHYSIOLOGICAL FUNCTIONS OF ENDOCRINE HORMONES

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Introduction

The realm of endocrine hormones encompasses a vast array of compounds that influence nearly every facet of human physiology. These hormones play pivotal roles in maintaining homeostasis, meeting metabolic demands, orchestrating development, and facilitating reproduction. This overview aims to delve into the glands responsible for hormone secretion, delineate the actions of these hormones, and pinpoint their target sites within the body. Additionally, it will shed light on several prevalent endocrine disorders linked to hormonal imbalances. While the coverage of diseases herein is not exhaustive, owing to the breadth of conditions and ongoing research, grasping the physiological intricacies of hormones and their implications in pathological states is paramount.

Issues of Concern

Hypothalamus

Posterior Pituitary (neurohypophysis) Hormones

The posterior pituitary, an extension of axonal projections from the supraoptic and paraventricular nuclei of the hypothalamus, harbors the storage sites for oxytocin and anti-diuretic hormone (ADH) within its axonal ends or Herring bodies.[1] Oxytocin secretion engenders a positive feedback loop during childbirth, augmenting contractions, and also exerts influence on lactation, a topic further elaborated in this article.[2]

ADH, also known as vasopressin, plays a crucial role in regulating blood volume and electrolyte balance, particularly sodium levels. Its primary function revolves around maintaining serum osmolarity, with ADH levels diminishing when osmolality falls below 280 mOsm/kg in a typical individual, prompting water excretion. Conversely, elevated plasma osmolality surpassing 280 mOsm/kg triggers an increase in ADH levels, facilitating water reabsorption. Apart from osmoreceptor stimulation, volume-sensitive receptors can also trigger ADH release, albeit only in response to a marked and sudden drop in pressure. Renin and norepinephrine manage smaller pressure changes instead.[3][4][5]

ADH exerts its effects via two distinct receptors, aiming to bolster water retention and elevate blood pressure. V2 receptors in the distal nephron promote water reabsorption by enhancing the number of aquaporin channels in principal cells of the collecting duct. Additionally, increased ADH levels activate V1 receptors, augmenting vascular resistance across the body.[6][7] Further insights into ADH functionality are provided in this article for a comprehensive understanding.[8]

Anterior Pituitary Affecting Hormones

The hypothalamic-pituitary-adrenal (HPA) axis serves as a blood portal system linking the hypothalamus and anterior pituitary, thereby regulating multiple hormones. An anatomical connection between the hypothalamus and the pituitary gland is facilitated by the

infundibulum. Within this structure, capillaries converge into portal veins, directly transporting hormones from the hypothalamus to the anterior pituitary, without entering the general circulation. Hormones released from the hypothalamus encompass corticotropin-releasing hormone, thyrotropin-releasing hormone, gonadotropin-releasing hormone, growth hormone-releasing hormone, somatostatin, prolactin-releasing hormone, and dopamine.[1]

Gonadotropin-releasing hormone (GnRH) originates from the hypothalamus and acts on the pituitary to regulate reproductive functions. Proper GnRH function relies on two crucial factors: adequate neuron migration during development and pulsatile secretion.[9] A limited number of hypothalamic neurons release GnRH, with fetal cells migrating to the olfactory bulb and tract, eventually reaching the mediobasal hypothalamus in the preoptic area and the arcuate nucleus. Notably, fetal cells in the olfactory region possess the ability to detect odorant stimuli and release GnRH. The significance of GnRH neuron migration was underscored in a case of an aborted fetus diagnosed with Kallmann syndrome, where neuropathological examination revealed arrested GnRH neurons at the cribriform plate, contrary to their expected migration to the hypothalamus.[10]

Moreover, the link between anosmia and GnRH deficiency is attributed to the close association of GnRH neurons with the olfactory bulb and tract. The pulsatile nature of GnRH neurons was demonstrated in vitro, showcasing regular yet discrete bursts of GnRH release, possibly indicating an intrinsic hypothalamic pulse generator's presence and emphasizing the pulse's significance.[9] GnRH pulsation plays a pivotal role in maintaining appropriate physiologic gonadotropin levels, with continuous GnRH administration leading to initial serum gonadotropin elevation followed by rapid desensitization and subsequent decrease.[11][12][13]

GnRH boasts a short half-life of merely 2 to 4 minutes and stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), collectively known as gonadotropins.[14] These hormones, along with sex steroids, exert both negative and positive feedback loops on GnRH pulsation, although the precise mechanisms remain incompletely understood. In addition to sex hormones, various molecules including opiates, gonadal steroids, kisspeptin, neurokinin B, catecholamines, neuropeptide Y, corticotropin-releasing hormone, galanin, dynorphin, and prolactin have been identified as influencers of GnRH. GnRH, LH, and FSH regulate critical functions in human sexual development, sex production, and fertility.[15][16] For further details, refer to the sections on LH and FSH, elaborated in this article.[17]

Corticotropin-releasing hormone (CRH) participates in the hypothalamic-pituitary-adrenal (HPA) axis. Originating in the paraventricular nucleus of the hypothalamus (PVH), CRH is released to stimulate the anterior pituitary gland, prompting the secretion of adrenocorticotrophic hormone (ACTH).[18]

Growth hormone-releasing hormone (GHRH) is a hypothalamic hormone that binds to pituitary receptors, initiating the release of growth hormone (GH). This binding triggers the activation of linked G proteins, fostering cAMP production. Consequently, GH is released, and somatotroph proliferation is stimulated. Although GH release appears pulsatory, the mechanism remains incompletely understood.[19]

Somatostatin exists in two biologically active forms, somatostatin-14 (S14) and somatostatin-28 (S28), comprising 14 and 28 amino acids, respectively. Synthesized by delta cells of the islets of Langerhans in the pancreas and scattered paracrine cells within the

gastrointestinal tract, somatostatin exhibits abundant presence in nervous tissue, notably in the spinal cord, brainstem, hypothalamus, and cortex.[20] Upon release, somatostatin's short half-life is notable, with approximately 50% removed from circulation within three minutes post-IV administration. Consequently, blood concentrations of somatostatin remain low, usually in sub-picomolar quantities. Activating G protein-coupled receptors, somatostatin reduces cAMP levels. Five receptor subtypes exist, each with tissue-specific distribution, collectively modulating various physiological functions.[21]

Binding to its receptor, somatostatin inhibits GH release from the pituitary gland.[22] Beyond GH inhibition, somatostatin exerts diverse physiological effects across multiple organs. In the brain, it demonstrates antinociceptive properties, while in the liver/gallbladder, it attenuates blood flow, inhibits gallbladder contraction, and suppresses bile duct secretion. Within the pancreas, somatostatin inhibits both endocrine and exocrine secretions, while within the gastrointestinal system, it inhibits salivary amylase, gastric acid, and gastrointestinal hormone secretions, delaying gastric emptying, slowing motility, impeding absorption, and decreasing splanchnic blood flow.[23][24]

Dopamine, renowned for its roles in psychiatric and neurological realms as a neurotransmitter, also functions as an endocrine hormone, secreted from the hypothalamus to the pituitary. Primarily, dopamine inhibits prolactin secretion. Reduced dopamine levels due to pathology or medication side effects lead to hyperprolactinemia and its associated pathophysiology.[26]

Thyrotropin-releasing hormone (TRH), composed of three peptides, initiates the regulation of TSH secretion within the HPA axis. Predominantly found in the PVH and median eminence of the hypothalamus, TRH also exists in the central nervous system, gastrointestinal tract, pancreatic islets, pituitary gland, and reproductive tracts. High levels or exogenous administration of TRH may stimulate additional hormones, particularly prolactin.[28][29][30][31]

Anterior Pituitary

Prolactin, a hormone synthesized by lactotrophs within the anterior pituitary gland, undergoes regulation by the hypothalamus in an inhibitory manner. Essentially, dopamine released from the hypothalamus serves to diminish prolactin secretion. Unlike most other hormones, which rely on stimulation signals from the hypothalamus for synthesis and release, prolactin's regulation follows a unique pattern. Consequently, severing the hypothalamic-pituitary-adrenal (HPA) axis leads to an increase in prolactin levels, while levels of other hormones decrease.[32]

Upon secretion, prolactin stimulates milk production in the mammary glands. During pregnancy, heightened estrogen levels act on the anterior pituitary to further enhance prolactin secretion, preparing the mammary glands for breastfeeding. However, concurrently elevated progesterone levels exert an inhibitory effect on prolactin at the breast. This explains why milk secretion commences only after birth, as the postpartum physiology entails a substantial decrease in progesterone levels, lifting the inhibition on prolactin.[33]

In cases of primary hypothyroidism, thyrotropin-releasing hormone (TRH) levels rise in an attempt to increase thyroid-stimulating hormone (TSH) levels. TRH can also act on the anterior pituitary to elevate prolactin levels. Anti-psychotics, acting as dopamine antagonists, disrupt the usual inhibitory effect of dopamine, resulting in elevated prolactin levels. In either scenario, along with several others such as prolactinoma, hyperprolactinemia ensues.

Elevated prolactin levels inhibit gonadotropin-releasing hormone (GnRH), leading to decreased pulsation and subsequently reduced levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Commonly observed symptoms include amenorrhea and infertility in both males and females.[35][36][37][38]

Thyroid-stimulating hormone (TSH), also known as thyrotropin, is synthesized and secreted by cells within the anterior pituitary gland, termed thyrotrophs. This hormone comprises two subunits: one alpha and one beta. While TSH shares the alpha subunit with three other hormones, its unique specificity within the human body is determined by the beta unit. The physiological effects of thyroxine (T4) and triiodothyronine (T3) tightly regulate TSH levels. Even minute increases in serum T3 and T4 lead to TSH inhibition, whereas slight decreases result in increased TSH levels. Furthermore, T3 and T4 levels play a role in modulating thyrotropin-releasing hormone (TRH) through negative feedback, providing another mechanism for regulating TSH levels.

Several factors influence changes in TSH levels, including the initial TSH level, the administered hormone (T3 or T4), and the dosage. Higher TSH levels take longer to decrease and gradually decline over several days. TSH levels respond more quickly to T3 than T4, and higher doses elicit a more rapid response. Inhibitors of TSH include somatostatin, dopamine, and glucocorticoids. Dopamine can cause a rapid decrease in TSH levels, and dopamine antagonists can acutely raise TSH levels. Patients in the intensive care unit (ICU) often exhibit altered TSH levels when receiving dopamine or dopamine antagonists. TSH is one of four endocrine hormones (hCG, TSH, LH, FSH) sharing the same alpha unit. Pathological states, such as choriocarcinoma, can induce hyperthyroidism symptoms because TSH receptors bind hCG due to the shared alpha unit.

TSH plays a crucial role in thyroid function, stimulating each step in hormone synthesis within the thyroid gland, influencing the expression of multiple genes, and potentially causing thyroid hyperplasia or hypertrophy. Upon binding to a plasma membrane receptor, TSH activates adenylyl cyclase, increasing cyclic adenosine monophosphate (cAMP) levels, thereby activating several protein kinases. Additionally, TSH stimulates phospholipase C, leading to increased phosphoinositide turnover, protein kinase C activity, and intracellular calcium concentration. However, the specific link between these steps and T3 and T4 synthesis, release, and other thyroid metabolic processes remains incompletely understood.

Growth hormone (GH), synthesized by pituitary somatotroph cells, is governed by five distinct genes that impact the final spliced mRNA hormone. The predominant form, a 22 kDa GH, comprises the majority, while a 20 kDa GH constitutes only 10%. Several factors influence GH production and release, with growth hormone-releasing hormone (GHRH) stimulating its release and somatostatin inhibiting it. Gender, age, nutrition, and insulin-like growth factor-1 (IGF-1) also exert modulatory effects on GH levels.

GH production initiates in the fetus, with maternal GH levels declining as placental GH levels increase. During puberty, characterized by extensive growth, GH levels peak at approximately 150 mcg/kg. However, with aging, GH levels decline, mirroring the decrease in body mass index. Every seven years, GH levels decrease by approximately 50%, reaching around 25 mcg/kg by the age of 55.

GH release occurs in a pulsatile manner, potentially due to reduced tonic inhibition of somatostatin and bursts of GHRH. Each day comprises ten pulsations, lasting 90 minutes, with intervals of 128 minutes. Gender influences GH pulsations, with men exhibiting more notable

pulsations compared to women, whose GH secretion appears more continuous. Peak GH secretions typically coincide with the onset of deep sleep, with average nighttime serum GH levels around 1.0 ± 0.2 ng/mL, contrasting with daytime levels of 0.6 +/- 0.1 ng/mL. Various factors such as IGF-1, leptin, age, obesity, and hyperglycemia inhibit GH release, while ghrelin, insulin-induced hypoglycemia, estrogen, dopamine, alpha-adrenergic agonists, and beta-adrenergic antagonists stimulate it. However, GHRH and somatostatin primarily dictate GH levels.

Upon binding to its receptor, primarily located in the liver, GH triggers a phosphorylation cascade via the JAK/STAT pathway. This cascade stimulates the liver to synthesize and secrete IGF-1, a critical protein induced by GH, believed to be responsible for most of GH's growth properties. GH exerts various effects, including stimulation of linear growth in children, increased lipolysis, enhanced protein synthesis, retention of phosphate, sodium, and water, and antagonism of insulin, with many of these actions attributed to GH acting in conjunction with IGF-1.

Adrenocorticotrophic hormone (ACTH) is a hormone secreted by the anterior pituitary gland in response to corticotropin-releasing hormone (CRH). Upon secretion, ACTH traverses the systemic circulation to exert its effects on the adrenal glands, specifically targeting the zona fasciculata and zona reticularis within the adrenal cortex. In the zona fasciculata, ACTH primarily stimulates the release of cortisol, a vital stress hormone. This stimulation occurs through the activation of the enzyme cholesterol desmolase, which catalyzes the initial step in converting cholesterol into various steroid hormones, including cortisol.

Furthermore, ACTH also plays a role in the production of androgens within the zona reticularis, which is a byproduct of cortisol synthesis. This dual action of ACTH underscores its significance in regulating adrenal function and the synthesis of essential steroid hormones necessary for various physiological processes.

Pineal Gland

Melatonin, a hormone synthesized within the pineal gland, originates from the amino acid tryptophan. Tryptophan undergoes hydroxylation and subsequent decarboxylation to form 5-hydroxytryptamine, commonly known as serotonin. In the presence of sunlight, serotonin is sequestered within pinealocytes, shielded from the action of monoamine oxidase, an enzyme responsible for serotonin conversion to melatonin. Conversely, in darkness, heightened sympathetic activity prompts the release of epinephrine, leading to serotonin release from pinealocytes. Concurrently, norepinephrine activates enzymes such as monoamine oxidase, serotonin-N-acetyltransferase, and hydroxyindole-O-methyltransferase. This cascade culminates in a rapid surge of melatonin levels from 2 to 10 pg/mL to 100 to 200 pg/mL. Melatonin's lipophilic nature facilitates its diffusion across cell membranes and the blood-brain barrier, enabling widespread cellular communication, particularly within the brain, where it modulates secondary messenger synthesis.

Melatonin exerts its effects through three identified receptors - M1, M2, and M3 - prominently expressed within the suprachiasmatic nucleus (SCN) of the hypothalamus. M1 receptor activation inhibits SCN neuron firing during the nighttime, while M2 receptor activity modulates the SCN's circadian rhythm. These actions are thought to contribute to melatonin's role in promoting sleep. However, M1 and M2 receptors are prone to desensitization, potentially necessitating higher doses of exogenous melatonin for sustained efficacy. The

melatonin cascade primarily governs sleep and circadian rhythms, with melatonin levels exhibiting a characteristic surge in the evening, peaking between 11 PM and 3 AM before declining prior to sunrise. While environmental light strongly influences circadian rhythm, it persists even in the absence of light exposure for extended periods.

Moreover, adjustments to new time zones do not immediately reset the circadian rhythm, highlighting its resilience. Melatonin production is predominantly localized to the pineal gland, as evidenced by the absence of significant melatonin levels and circadian rhythm in individuals post-pinealectomy. These observations underscore the pivotal role of melatonin in regulating circadian rhythms and facilitating sleep initiation and maintenance.

Thyroid Gland

Thyroid hormones, T3 and T4, play pivotal roles across the lifespan. During childhood development, they facilitate the maturation of various bodily systems, particularly the brain. In adulthood, they orchestrate metabolic processes and contribute to the functioning of nearly all organs. Given their multifaceted importance, maintaining a steady supply of thyroid hormones is essential, with serum levels meticulously regulated to prevent pathological deviations. Two mechanisms govern thyroid hormone production: hormonal pathways with negative feedback loops and hormone utilization by extrathyroidal tissues, influenced by factors such as nutrition, hormones, and illness.

The first mechanism safeguards against hyper- or hypo-secretion of thyroid hormones, while the second mechanism enables tissue-specific responses to rapid changes. As outlined in the TSH section, the synthesis of T3 and T4 hinges on iodide oxidation and its incorporation into tyrosine residues within the colloid. Thyroglobulin, a glycoprotein, plays a crucial role by integrating into exocytotic vesicles, which subsequently fuse with the apical cell membrane to facilitate iodination and hormone synthesis. Release into the extracellular fluid necessitates the resorption of thyroglobulin into thyroid follicular cells, culminating in hormone secretion via phagolysosome formation.

The majority of T4 (99.95%) and T3 (99.5%) circulate in a bound state, rendering them metabolically inactive. Principal binding proteins include thyroxine-binding globulin (TBG), transthyretin (TTR), albumin, and lipoproteins, in descending order of prevalence. Despite the minimal proportion of free T4 and T3 in circulation, changes in binding protein concentrations exert significant effects on total serum T4 and T3 levels. However, alterations in binding proteins do not impact free hormone concentrations or the rate of T4 and T3 metabolism.

Thyroxine (T4), a hormone with lower metabolic activity, is exclusively synthesized within the thyroid gland. Its daily production rate ranges from 80 to 100 mcg, with approximately 10% being degraded each day. Roughly 80% of T4 undergoes deiodination, where 40% converts to triiodothyronine (T3), another 40% converts to reverse T3 (rT3), and the remaining 20% conjugates to tetraiodothyroacetic acid.

The conversion of T4 to T3 in peripheral tissues is facilitated by the enzyme 5'-deiodinase. Among T4 metabolites, T3 is the primary active form, while others remain inactive. This conversion process is regulated independently in extrathyroidal tissues, allowing T3 production to vary irrespective of the pituitary-thyroid state.

Tri-iodothyronine (T3) serves as the primary metabolic hormone originating from the thyroid gland, steering metabolic and organ processes. Roughly 80% of T3 production occurs in extrathyroidal tissues through the deiodination of T4, while the remaining 20% is

synthesized within the thyroid gland. Daily T3 production ranges from 30 to 40 mcg, yet the extrathyroidal reserve of T3 totals approximately 50 mcg. The proportion of T3 generated throughout the body from T4 varies significantly across different tissues. Tissues like the anterior pituitary and liver possess elevated levels of T3 nuclear receptors, rendering them more responsive to serum T3.

T3 functions by modulating gene transcription, exerting widespread effects on protein synthesis and substrate turnover in nearly all tissues. Nuclear actions of T3 hinge upon several factors, including hormone availability, thyroid hormone nuclear receptors (TRs), receptor cofactor availability, and DNA regulatory elements. While T3 typically enters tissues through simple diffusion, active transport mechanisms facilitate its entry into cells in the brain and thyroid. T3 exerts tissue-specific actions determined by local T3 production and the abundance and distribution of TR isoforms, such as TR-alpha-1, TR-alpha-2, TR-beta-1, TR-beta-2, and TR-beta-3. Although studies on TR isoforms remain limited, evidence suggests distinct functions even within the same tissue due to their regional or cell-specific distributions.

Insights into TR isoforms primarily stem from studies on knockout mice with TR gene mutations. Mice lacking TR-alpha exhibit symptoms like poor feeding and growth, reduced heart rate, decreased body temperature, and impaired bone mineralization. In contrast, mice with TR-beta gene inactivation display indicators of normal serum TSH levels, elevated serum T4 concentrations, and thyroid gland hyperplasia. Knockout mice devoid of both TR-alpha and beta genes demonstrate thyroid hyperplasia and significantly elevated serum T4, T3, and TSH levels compared to normal.

Upon binding to TR on the nucleus, T3 modulates gene expression, targeting genes with specific DNA sequences that bind TR with high affinity. The Human Genome Project has provided critical data enabling the identification of these sequences, crucial for effective T3-dependent gene activation. Without these specific DNA sequences, the activation of T3-dependent genes may be minimal or entirely absent.

Different tissues harbor one of three deiodinases within the periphery, facilitating the conversion of the prohormone T4 to active T3. The expression of these three enzymes depends on a specific pattern of development and tissue type.

- Type 1 5’-deiodinase (Dio1) is predominantly found in the liver, kidneys, and muscle tissues. Reduced activity of Dio1 has been observed in hypothyroid individuals.
- Type 2 5’-deiodinase (Dio2) is more prevalent in the cerebral cortex, brown fat, and the pituitary gland in rodents. In humans, Dio2 is also expressed in skeletal muscle, heart, and thyroid tissues. Dio2 contributes to the majority of circulating T3 in humans and has been found to increase in subjects with hypothyroidism and iodine deficiency.
- Type 3 5’-deiodinase (Dio3) plays a role in the inactivation of T4 and is primarily found in the placenta, skin, skeletal muscle, and the developing brain. It is crucial for sensory development, particularly within the inner ear. During human development, Dio3 is initially expressed, but as Dio1 and Dio2 levels rise, Dio3 expression decreases.

It is widely recognized that T4 and T3 exert broad effects and can impact almost every organ system in the body. Specifically, three major areas of influence include bones, the heart, and the regulation of metabolism.

- Bones – Infants with congenital hypothyroidism who do not receive hormone replacement therapy may experience delayed epiphyseal development and impaired growth. Similar observations have been noted in individuals with thyroid hormone resistance. While all thyroid hormone receptor (TR) isoforms are expressed in bones, abnormal bone development has been observed in TR-alpha and alpha/beta knockout mice.
- Heart – Individuals with T3 resistance typically exhibit elevated T3 levels, leading to tachycardia. This suggests that resistance to T3 may not necessarily extend to cardiac tissues. Patients with TR-beta mutations often present with similar symptoms, a notion supported by studies on T3-beta knockout mice which also lack cardiac resistance to T3.
- Metabolism Regulation – T3 plays a key role in regulating metabolic rate and can influence modest changes in body weight. Humans with TR-beta mutations and T3 resistance typically show increased T3-alpha activity, resulting in heightened feeding behavior and enhanced fatty acid oxidation. T3 also affects glucose metabolism by promoting its uptake. Dysfunction of Dio2 has been associated with glucose intolerance. Although not extensively studied, individuals with impaired mitochondrial oxidative metabolism, such as those with metabolic syndrome and type 2 diabetes, may experience reduced T3 hormone action. The consequences of disrupted metabolism will be further explored in discussions on thyroid hormone pathology.

Parathyroid

Parathyroid hormone (PTH) plays a pivotal role in maintaining the balance of calcium and phosphate levels in the body. Initially synthesized as pre-pro-PTH, a 115-amino acid precursor, it undergoes successive cleavage steps within parathyroid cells to yield pro-PTH, containing 90 amino acids, and finally the active form of PTH, consisting of 84 amino acids. This 84-amino acid variant represents the primary stored, secreted, and biologically active form of PTH.

Short-term regulation of serum calcium levels is exclusively mediated by PTH, while on a long-term basis, PTH facilitates the conversion of calcidiol to calcitriol within renal tubular cells.

PTH exhibits rapid clearance from the bloodstream by the kidney and liver, with intact PTH having a brief half-life of 2-4 minutes. Upon cleavage, it generates active amino fragments (PTH 1-34) and inactive carboxyl fragments. Notably, calcium exerts tight control over PTH release, synthesis, and degradation.

Even minor fluctuations in serum ionized calcium concentrations, as small as 0.1 mg/dL, trigger corresponding adjustments in PTH secretion. This responsiveness is facilitated by highly sensitive calcium-sensing receptors (CaSR) on the surface of parathyroid cells. Activation of CaSRs inhibits PTH release, while deactivation during hypocalcemia stimulates parathyroid cells to secrete PTH.

CaSRs play a pivotal role in mediating various actions of PTH, including exocytosis into the bloodstream, modulation of intracellular PTH breakdown, regulation of PTH gene expression, and proliferation of parathyroid cells. While calcium serves as the primary driver of PTH secretion, other molecules such as extracellular phosphate, calcitriol, and fibroblast growth factor 23 (FGF23) also influence PTH release.

The principal receptor for PTH, referred to as PTH1R, exhibits affinity for PTH, PTH-related protein (PTHrP), and PTH1-34, demonstrating robust expression in bone and kidney tissues, with potential presence in other organs such as the breast, heart, skin, pancreas, and vascular tissue. Upon activation of PTH1R, multiple intracellular signaling pathways including cAMP, phospholipase C pathway, protein kinase C, and intracellular calcium are engaged to mediate the effects of PTH.

The biological actions of PTH encompass several key processes: enhanced bone resorption, which occurs rapidly within minutes; increased gastrointestinal absorption of calcium mediated by calcitriol over a longer timeframe of 24 hours or more, facilitated by PTH-induced hydroxylation of calcidiol to calcitriol; and reduced urinary excretion of calcium, which occurs promptly within minutes.

Delving deeper into PTH's actions on bone, two primary phases orchestrate the elevation in calcium levels. Firstly, PTH promptly mobilizes calcium from skeletal reservoirs. Subsequently, PTH stimulates bone resorption, leading to the liberation of calcium and phosphate, although these effects are not immediate. Additionally, the kidney participates in calcium reabsorption through distinct mechanisms across different nephron regions. For instance, in the proximal tubule, calcium is passively reabsorbed via favorable electrical gradients, while in the distal nephron, active reabsorption mechanisms are employed. The cumulative effect of these concurrent pathways ultimately culminates in a rise in calcium levels, contributing to the restoration of systemic homeostasis.

Pancreas

Insulin exerts direct and indirect effects on various tissues, with a focus here on adipose tissue, muscle, and the liver. This peptide hormone, consisting of 51 amino acids, is synthesized and released by the pancreatic beta cells. Upon binding to a heterotetrameric receptor on the cell membrane, insulin initiates its action. This receptor comprises two alpha subunits responsible for insulin binding and two beta subunits that transduce the signal. Through intricate cell signaling pathways, insulin plays a pivotal role in regulating metabolic functions. Disruptions in insulin signaling, resistance, or reduced insulin levels can lead to a range of pathologies, as discussed further in the pathology section.

Insulin secretion can be either stimulated or inhibited by various factors. Glucose, mannose, leucine, and vagal stimulation promote insulin secretion, while alpha-adrenergic effects, somatostatin, and certain drugs inhibit it.

A key function of insulin is to regulate glucose levels, which can originate from gluconeogenesis, oral intake, or glycogenolysis. Once glucose enters cells, it undergoes either storage as glycogen or conversion to pyruvate through glycolysis. Insulin modulates glucose metabolism through several mechanisms, including stimulation of glycogen synthesis, enhancement of glucose transport into muscle and adipose tissue, inhibition of glycogenolysis and gluconeogenesis, and promotion of glycolysis in muscle and adipose tissue. While many tissues can produce glucose internally, only the kidney and liver possess glucose-6-phosphatase, necessary for releasing glucose into the bloodstream. In individuals without glucose-related disorders, the liver accounts for 80 to 90% of glucose production, making it a primary target for insulin action. Insulin influences liver function through both direct and indirect pathways. Directly, insulin inhibits hepatic glycogen phosphorylase, the enzyme responsible for glycogenolysis, thereby reducing glucose output. Indirectly, insulin decreases the availability of glucose precursors and suppresses glucagon secretion. Studies, such as

insulin infusion experiments in dogs, have elucidated the predominant effects of insulin on hepatic glucose metabolism, highlighting both direct and indirect pathways, with the latter becoming more pronounced with substantial insulin infusion.

Glucose utilization hinges on cellular uptake facilitated by glucose transporters, including GLUT-1,2,3,4, and 5. Among these, GLUT-4 takes precedence in muscle and adipose tissues, residing in the cytoplasm until insulin signaling prompts its translocation to the cell membrane. In a euglycemic state, insulin-mediated glucose uptake predominantly occurs in muscle tissue, while adipose tissue accounts for less than 10%, largely due to insulin's suppression of lipolysis. Increased glucose uptake by muscle is necessitated when free fatty acids are unavailable for energy. Insulin optimizes muscle glycolysis by enhancing hexokinase and 6-phosphofructokinase activity.

Postprandially, insulin curbs lipolysis and fosters triglyceride storage in adipocytes through three primary mechanisms. Firstly, it heightens the clearance of triglyceride-rich chylomicrons by upregulating lipoprotein lipase expression specifically in adipose tissue. In contrast, in muscle, insulin impedes lipoprotein lipase. Secondly, insulin promotes the re-esterification of fatty acids into triglycerides within adipocytes. Finally, it directly inhibits lipolysis. Overall, insulin-mediated fat metabolism significantly curtails hepatic gluconeogenesis and glucose release by impeding the delivery of fatty acids to the liver.

In instances of deficient insulin levels, such as prolonged fasting or uncontrolled diabetes mellitus, fat mobilization ensues to meet metabolic demands. Excessive fatty acids overwhelm the liver, leading to ketone body production through incomplete beta-oxidation. Ketoacids serve as alternative fuel for extrahepatic tissues like skeletal muscle and the heart, and eventually, even the brain during prolonged fasting. Insulin plays a crucial role in regulating ketone levels by inhibiting lipolysis, thereby limiting the availability of fatty acids for ketone body synthesis. Additionally, insulin directly curbs ketogenesis in the liver and enhances peripheral clearance of ketone bodies.

Regarding protein metabolism, as mentioned earlier, insulin's inhibition of gluconeogenesis ensures the availability of amino acids for protein synthesis. Insulin facilitates the uptake of amino acids into the liver and skeletal muscle and enhances ribosomal quantity and efficiency. Moreover, insulin curtails protein breakdown, exerting influence over approximately 40% of proteolysis and resulting in a net increase in protein synthesis.

Insulin's impact extends to modulating various hormones in the body. Pancreatic islet cells contain alpha, beta, and delta cells, secreting glucagon, insulin, and somatostatin, respectively. These hormones exert paracrine effects on neighboring cells. Notably, insulin first targets alpha cells, suppressing glucagon release and intensifying its metabolic effects. Additionally, in hyperglycemic conditions, somatostatin secretion further inhibits glucagon release from alpha cells, contributing to glucose level reduction.

Beyond its role in energy metabolism, insulin serves vital functions with clinical significance, as aberrant insulin responses can lead to diverse pathologies. Insulin influences steroidogenesis, fibrinolysis, vascular function, and growth, underscoring its multifaceted physiological importance.

Glucagon, a 29-amino acid peptide, is released from the alpha cells of the islets of Langerhans. It acts in opposition to insulin, aiming to elevate glucose levels in the body. Glucagon secretion is prompted by protein ingestion, hypoglycemia, and physical exercise. Its mechanisms involve stimulating glycogenolysis, leading to the conversion of stored glycogen

into glucose. Additionally, glucagon facilitates gluconeogenesis, wherein precursor molecules such as amino acids and glycerol are utilized to generate glucose in the liver.

Adrenal Glands

Situated just above the kidney, the adrenal gland synthesizes various hormones, including aldosterone, cortisol, DHEA, norepinephrine, and epinephrine. These hormones are produced in distinct regions of the adrenal gland. The cortex comprises three layers: the zona glomerulosa, zona fasciculata, and zona reticularis, which secrete aldosterone, cortisol, and DHEA, respectively. Meanwhile, the adrenal gland's medulla, composed of chromaffin cells, is responsible for the synthesis and release of norepinephrine and epinephrine.

Cortisol- a glucocorticoid hormone synthesized in the adrenal gland's zona fasciculata, is stimulated by ACTH. Its primary function is to elevate glucose levels in the body by promoting gluconeogenesis, lipolysis, and proteolysis. Additionally, cortisol induces insulin resistance to sustain elevated glucose levels, which can contribute to the development of diabetes mellitus at high levels. Apart from its role as a glucocorticoid, cortisol possesses other properties that make it useful as a medication in hospitalized patients. It can enhance appetite, elevate blood pressure, inhibit bone formation, and notably, suppress inflammatory and immune responses. Cortisol operates within a negative feedback loop that acts on the hypothalamus, anterior pituitary, and adrenal gland to inhibit the release of CRH, ACTH, and cortisol, respectively.

Aldosterone plays a critical role as a mineralocorticoid hormone within the renin-angiotensin system (RAS), crucial for regulating cardiac, renal, and vascular physiology. The RAS pathway initiates with renin cleaving angiotensinogen into the inactive angiotensin I, subsequently converted to angiotensin II primarily by angiotensin-converting enzyme (ACE) action, notably in the lungs. Angiotensin II triggers the release of aldosterone from the zona glomerulosa of the adrenal gland via angiotensin II type 1 receptors (AT1Rs).

While the RAS pathway serves as the primary stimulus for aldosterone, small levels of angiotensin II produced by the adrenal gland, as well as ACTH from the anterior pituitary, and potassium, also stimulate aldosterone release. Aldosterone's primary action occurs in the kidney, where it enhances the expression of sodium channels on the epithelium within the distal tubule. Consequently, this augments sodium reabsorption, along with water, while promoting potassium secretion. The outcome is an expansion in extracellular fluid volume, reduction in serum potassium, and elevation in blood pressure.

Traditionally considered a rare cause of hypertension, primary aldosteronism's prevalence has been revealed to be substantially higher through studies over the past 15 years. The initial diagnostic evaluation for primary aldosteronism typically involves measuring renin: aldosterone ratios, aiding in determining the need for further investigation in patients suspected of the condition.

Adrenal Androgens, primarily dehydroepiandrosterone (DHEA) and DHEA sulfate, are synthesized in the adrenal gland as byproducts of cortisol synthesis. Their production is chiefly stimulated by ACTH. While DHEA and DHEA sulfate possess minimal inherent androgenic properties, their excess secretion is a hallmark of congenital adrenal hyperplasia (CAH). A fraction of these hormones is converted to androstenedione, and subsequently to testosterone (and possibly estrogen) in both the adrenals and peripheral tissues. It is upon this conversion that the physiological effects of androgens manifest, as seen in the endocrine sex hormones. Therefore, it is not DHEA and DHEA sulfate themselves that lead to virilization

in young females; rather, the elevated levels are converted to more potent androgens, resulting in the classic phenotype observed in CAH.

Typically, DHEA and DHEA sulfate levels rise during puberty and for several years afterward in both sexes. They peak in the third decade of life before gradually declining, with adrenal androgens at about 25% of their peak levels by age 80, a phenomenon known as adrenopause, whose significance remains uncertain. In males, adrenal testosterone accounts for less than 5% of total serum testosterone. However, in females, a considerable portion of serum testosterone in the menstrual cycle, particularly during the follicular phase, is derived directly or indirectly from adrenal androgens.

Epinephrine (adrenaline) and n**orepinephrine** (noradrenaline) – due to their shared origin in the adrenal gland medulla and numerous similarities, these two hormones will be addressed together. By exploring the effects of stimulation on alpha-1, beta-1, and beta-2 receptors, we can better understand the actions of epinephrine and norepinephrine. In clinical contexts, the use of these hormones varies depending on dosage and the patient's condition.

1. Alpha-1 – Activation triggers the IP3-DAG cascade, leading to heightened intracellular calcium levels. Peripheral artery stimulation induces vasoconstriction, elevating resistance and subsequently raising mean arterial pressure (MAP). Alpha-1 also constricts veins, enhancing venous return to the heart. Additional effects include mydriasis (pupil dilation) and urine retention through contraction of the urethral sphincter and prostatic smooth muscle.
2. Beta-1 – Predominantly found in the heart, activation of these receptors increases inotropy and chronotropy without impacting vessels. Beta-1 stimulation can also boost renin release, contributing to blood pressure elevation.
3. Beta-2 – Activation of these receptors in blood vessels leads to vasodilation, reducing systemic vascular resistance (SVR) and lowering diastolic blood pressure. In the lungs, beta-2 activation induces bronchodilation, while in the liver, it promotes gluconeogenesis. Additionally, beta-2 stimulation in the eye can increase aqueous humor production.

Epinephrine binds and activates all three receptors, but the predominant receptor affected depends on the administered dose. At lower doses, beta receptor action prevails, leading to increased cardiac output (CO) due to beta-1's inotropic and chronotropic effects. While alpha-1 stimulation typically induces vasoconstriction, beta-2's vasodilatory effect offsets this. Consequently, all three receptors being stimulated result in elevated CO, decreased systemic vascular resistance (SVR), and variable effects on mean arterial pressure (MAP). In contrast, high-dose epinephrine primarily stimulates alpha-1, leading to increased SVR and CO. Released into the bloodstream during periods of intense stress or "fight or flight" situations, epinephrine, aptly named adrenaline, provides a surge of energy facilitated by these physiological effects.

Norepinephrine acts on both alpha-1 and beta-1 receptors, with alpha-1 stimulation predominating. This results in potent vasoconstriction and a mild increase in cardiac output. Although a slight chronotropic effect is observed, reflex bradycardia due to increased MAP counteracts it. Norepinephrine secretion often occurs alongside epinephrine release in response to stressors. However, there are instances when these hormones are secreted

independently. While norepinephrine and epinephrine have additional functions beyond the endocrine system, these are beyond the scope of this discussion on endocrine hormones.

Appetite Regulation

Ghrelin, often dubbed the "hunger hormone," is a 28 amino-acid peptide primarily synthesized in the stomach, particularly in the gastric fundus where oxyntic gland P/D1 cells reside. These cells come in two types: the open type, exposed to the stomach lumen, secretes directly into the stomach contents, while the closed type, found near the lamina propria, secretes directly into the vasculature. While ghrelin is also found in the pancreas, placenta, kidney, and pituitary, its levels are significantly lower there. Ghrelin receptors, known as growth hormone secretagogue receptors (GHS-R), come in two forms: GHS-R1a and GHS-R1b. GHS-R1a, present in both the central nervous system and peripheral tissue, regulates food intake and satiety. However, GHS-R1b's function remains unclear as it lacks links to the same G protein complex as GHS-R1a.

Ghrelin levels surge during fasting, starvation, and anorexia, with additional spikes noted before meals. Nutrients, particularly carbohydrates, protein, and lipids, suppress ghrelin secretion, primarily through non-vagal signals from the stomach and intestines.

Primarily, ghrelin stimulates growth hormone (GH) secretion, possibly even GHRH itself, further enhancing GH release. Consequently, it increases appetite and promotes a positive energy balance, alongside the effects of GH. Moreover, ghrelin acts locally in the stomach to enhance gastric contraction and facilitate stomach emptying. Notably, osteoblasts express GHS-R1a, suggesting a potential direct effect on bone formation, which aligns with GH's known impact on bone mass and formation. Defects in GHS-R have been associated with short stature, underscoring its significance in bone formation.

Ghrelin has been observed to increase meal frequency without affecting meal size. Additionally, it plays a role in regulating long-term body mass. In individuals with a normal BMI, ghrelin levels typically range from 550 to 650 pg/mL. Conversely, obese individuals exhibit lower levels ranging from 200 to 350 pg/mL, suggesting an inverse correlation between ghrelin and BMI. During fasting, anorexic, and cachectic states, ghrelin levels are notably elevated, often exceeding 1000 pg/mL on average. Interestingly, decreased ghrelin levels in obese individuals are associated with gastritis, regardless of the presence of Helicobacter pylori.

Leptin, known as the "satiety hormone," operates in contrast to ghrelin by suppressing appetite. It's a 167 amino acid protein primarily synthesized from the ob gene and predominantly expressed in adipocytes. Leptin exerts its effects through binding to various isoforms of leptin receptors (LEPRs), including LEPR-a to LEPR-f. Notably, the longest isoform, LEPR-b, is present in multiple organs, particularly in the brain's hypothalamic and brainstem nuclei. Mutations in this isoform have been linked to severe obesity.

In individuals with normal BMI, heightened leptin levels have been associated with reduced food intake. However, in obese individuals, the response to leptin is attenuated, even with exogenous leptin administration at supraphysiological levels. Leptin production and circulation correlate directly with the percentage of body fat. Overeating can elevate leptin levels by approximately 40% in just 12 hours, while fasting can lead to a decrease of 60 to 70% in 48 hours, reaching up to 80% in 72 hours. Regular food intake prompts a feedback loop where leptin interacts with adipose tissue, influencing adipocytes to secrete leptin based

on body adipose percentage. Leptin secretion is influenced by gender, with estrogen boosting leptin levels in females, while androgens diminish serum leptin levels in males. Additionally, leptin has implications in nutrition-immune function relationships, with low leptin levels seen in prolonged starvation or cachexia associated with Th1/Th2 imbalance, low CD4 counts, and decreased T-cell production.

Furthermore, leptin has both direct and indirect effects on bone density, although studies have presented conflicting findings regarding its correlation with bone density. The precise impact of leptin on bone remains uncertain, prompting ongoing research in this area.

Clinical Significance

Comprehending the intricate interplay of hormones crucial for maintaining strict homeostatic balance is essential. A solid understanding of endocrine physiology often simplifies the diagnosis of pathology. When hormone levels deviate from the norm, they manifest in distinct ways—either through deficiency or excess action—providing vital clues for diagnosis. This understanding enables healthcare providers to narrow down the possible causes, order relevant tests and imaging, and devise appropriate treatment strategies.

However, diagnosing hormonal disorders isn't always straightforward due to the intricate relationships between hormones. Hormonal imbalances can influence other hormones, leading to a cascade of symptoms. For instance, elevated prolactin levels can inhibit GnRH, resulting in amenorrhea and infertility due to reduced FSH and LH levels.

While it might seem intuitive to focus solely on reproductive organs or their associated hormones when assessing dysfunction, the underlying cause may often lie elsewhere. Hyperprolactinemia, for example, could be the underlying cause rather than a primary reproductive issue. Additionally, in rare cases, hormone resistance syndromes should be considered, particularly when there's a discrepancy between elevated hormone levels and the function of target organs, such as in receptor defects like nephrogenic diabetes insipidus or pseudohypoparathyroidism.

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